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(71) Applicant *(for all designated States except US)*: A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L. [IT/IT]; Via Sette Santi, 3, I-50131 Firenze (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SALIMBENI, Aldo [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT). PALEARI, Fabio [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT). SCOLASTICO, Carlo [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT). CRISCUOLI, Marco [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

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(54) Title: BICYCLIC LACTAM DERIVATIVES AS THROMBIN INHIBITORS

(57) Abstract

Bicyclic lactams containing an arginine residue, which can be of use in therapy as thrombin inhibitors, are disclosed.

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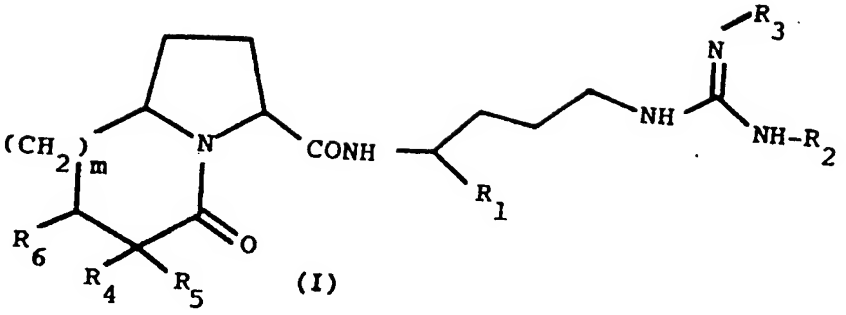
# BICYCLIC LACTAM DERIVATIVES AS THROMBIN INHIBITORS

The present invention relates to bicyclic lactam derivatives with antithrombotic activity, the processes for the preparation thereof, pharmaceutical compositions containing them and the use thereof as therapeutical agents.

The object of the invention are novel bicyclic lactam derivatives having an arginine residue, the salts and hydrates thereof, in diastereomerically pure forms or as stereoisomeric mixtures, having inhibitory activity on some serine-proteases. More particularly, the compounds turned out to be active in inhibiting the action of the enzyme thrombin and therefore can be used as antithrombotic, antiaggregating or anticoagulant agents. The novel derivatives are characterized by having a bicyclic lactam residue which is capable of acting as a conformationally constricted analogue of a peptidic sequence, such as the one consisting of Phe-Pro-Arg, which is present in fibrinogen structure and is considered important for recognizing the thrombin active site. A number of examples of thrombin inhibitors are known, which are based on structural changes of the sequence Phe-Pro-Arg, see for example Patents US n° 4,478,745, US n° 4,399,065, EP 526,877, US n° 697,987 and papers by Bajusz et al., J. Med. Chem., 1990, 33, 1729-1735 and Kettner et al., Thromb. Res., 1979, 14, 969-973.

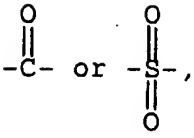
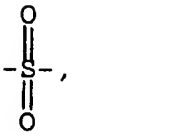
The compounds of the invention have general formula I:



(I)

wherein:

- m is 0, 1, 2 or 3;
- $R_1$ is a group of formula -CHO, $-CH_2OH$, COOH, $-B(OH)_2$;
- $R_2$, $R_3$ are independently hydrogen, $COOR_7$, $C_1$-$C_4$ alkyl, benzyl, $-NO_2$;
- $R_4$, $R_5$ are independently hydrogen, $NR_8R_9$, straight or branched $C_1$-$C_7$ alkyl, $C_3$-$C_7$ cycloalkyl or an arylalkyl or heteroarylalkyl group, optionally substituted at the ring with one or more substituents such as halogen (Cl, Br, I), methoxyl, trifluoromethyl, straight or branched $C_1$-$C_7$ alkyl;
- $R_6$ is hydrogen, straight or branched $C_1$-$C_7$ alkyl, $C_3$-$C_7$ cycloalkyl or an aryl, heteroaryl, arylalkyl or heteroarylalkyl group, optionally substituted at the ring with one or more substituents such as halogen (Cl, Br, I), methoxy, trifluoromethyl, straight or branched $C_1$-$C_7$ alkyl;
- $R_7$ is $C_1$-$C_4$ alkyl, benzyl;
- $R_8$, $R_9$ are independently hydrogen, straight or branched $C_1$-$C_7$ alkyl or a group of general formula -W-Q wherein:

- W can be a group  or  ,

- Q can be a phenyl, benzyl, naphthyl, quinolyl, naphthylmethyl, tetrahydroquinolyl, tetrahydroisoquinolyl group, optionally substituted with one or more groups such as halogen (Cl, Br, I), straight or branched $C_1$-$C_7$ alkyl, methoxy, trifluoromethyl.

The compounds of the invention form, with various both inorganic and organic acids, salts which also are an object of this invention. Said salts include for example hydrochlorides, hydrobromides, sulfates, phosphates, maleates, fumarates.

Examples of $C_1$-$C_7$ alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl.

Examples of $C_3$-$C_7$ cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl.

Aryl groups are preferably phenyl and naphthyl. Heteroaryl groups are preferably thienyl, quinolyl or tetrahydroquinolyl. Examples of arylalkyl groups include benzyl and phenethyl, preferably benzyl. Examples of heteroarylalkyl groups comprise furylmethyl and thienylmethyl.

Examples of $R_4$ and/or $R_5$ groups are benzyl, thienylmethyl, amino, acetylamino, methylamino, dimethylamino, t-butoxycarbonylamino, benzyloxycarbonylamino, naphthylsulfonylamino, quinolylsulfonylamino, benzylsulfonylamino, naphthylmethylsulfonylamino, ethylamino, tetrahydroquinolylsulfonylamino.

Examples of $R_6$ groups are phenyl, thienyl, methyl,

ethyl.

Preferred compounds of formula I are those wherein m is 2, $R_1$ is -CHO and $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ have the meanings reported above.

Other preferred compounds of formula I are those wherein m is 1, $R_1$ is -CHO and $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ have the meanings reported above.

Particularly preferred compounds are those wherein $R_4$ and/or $R_5$ are an arylalkyl, heteroarylalkyl group optionally substituted as indicated above, or a $NR_8R_9$ group other particularly preferred compounds are those wherein $R_6$ is an aryl, heteroaryl, arylalkyl or heteroarylalkyl group, optionally substituted as indicated above, and $R_4$ and/or $R_5$ are a protected amino group. Most preferred compounds are the following:

- $N^a$-[[6-acetylamino-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^a$-[[6-methylamino-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^a$-[[6-[(benzylsulfonyl)amino]-octahydropyrrolo-[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^a$-[[6-[[[(naphthalen-1-yl)methyl]sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^a$-[[6-[[[(naphthalen-2-yl)methyl]sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^a$-[[6-[[(3-methylquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^a$-[[6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl]-

L-arginine aldehyde,

- $N^{\alpha}$-[[6-[(thiophen-2-yl)methyl]-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^{\alpha}$-[[6-[(naphthalen-2-yl)methyl]octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^{\alpha}$-[[6-[(naphthalen-1-yl)methyl]-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,
- $N^{\alpha}$-[[6-acetylamino-6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

-$N^{\alpha}$-[[6-benzyl-6-methylamino-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

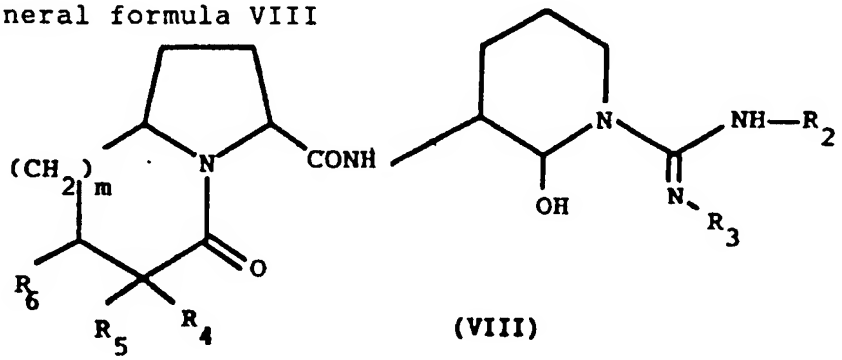
-$N^{\alpha}$-[[6-benzyl-6-[(t-butoxycarbonyl)amino]-octahydroindolizin-5-one-3-yl]-L-arginine aldehyde,

-$N^{\alpha}$-[[6-amino-7-phenyl-octahydroindolizin-5-one-3-yl]-carbonyl]-L-arginine aldehyde,

-$N^{\alpha}$-[[6-(methylamino)-7-phenyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

-$N^{\alpha}$-[[6-(acetylamino)-7-phenyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde.

According to the invention, compounds of general formula I can be obtained starting from intermediates of general formula VIII

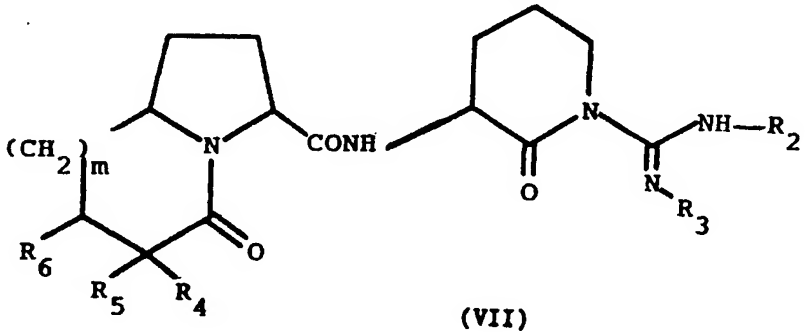



(VIII)

wherein $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and m have the meanings reported above, removing the protective group(s) on the guanidine residue. The deprotection reaction, where $R_2$

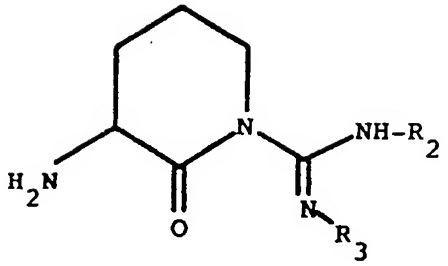
($R_3$) represents a benzyl, nitro or benzyloxycarbonyl group, can be carried out in solvents such as $C_1$-$C_4$ alcohols, ethyl acetate, tetrahydrofuran, in the presence of a Pd or Pt catalyst on charcoal under hydrogen atmosphere, or, where $R_2$ ($R_3$) is a t-butoxycarbonyl group, by treatment with strong organic or inorganic acids in apolar solvents such as dioxane or tetrahydrofuran.

The intermediates of general formula VIII can be obtained from compounds of general formula VII



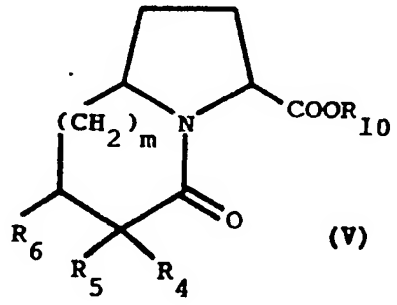
(VII)

wherein $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and m have the meanings reported above, by reduction with, for example, metal hydrides, such as $LiAlH_4$, $NaBH_4$, $NaCNBH_4$, $LiBH_4$, $LiBEt_3H$, in both apolar and polar solvents, such as ethyl ether, tetrahydrofuran or $C_1$-$C_4$ alcohols, at temperatures from -20°C to room temperature. Intermediates of general formula VII can be obtained by condensation of compounds of general formula VI, the preparation of which is described in literature (see for example Balasubramanian N. et. al, J. Med. Chem., 1993, 36, 300-303) and wherein $R_2$ and $R_3$ have the meanings reported above,



(VI)

with compounds of general formula V, wherein $R_4$, $R_5$, $R_6$, and m have the meanings reported above and $R_{10}$ is hydrogen.

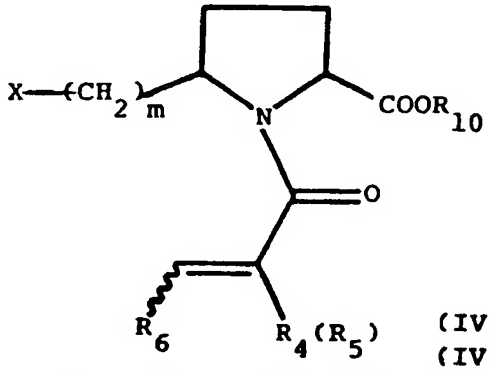


(V)

The condensation reaction can be carried out according to one of the procedures known in literature, used to form peptide or amido bonds (see for example Bodanszky M., Peptide Chemistry, chapter V, pag. 55-72, Springer-Verlag Editor).

By way of example, dicyclohexylcarbodiimide, diphenyl phosphoryl azide can be used as carboxy-activating agents, or mixed anhydrides can be prepared by reaction with alkyl chloroformates; subsequently the intermediates can be reacted with the amino derivative of general formula VI, in solvents such as dichloromethane, chloroform, tetrahydrofuran, dimethyl-formamide, at temperatures generally ranging from 0°C to room temperature.

Compounds of general formula V can be obtained by cyclization starting from intermediates of general formula IV, wherein $R_4$ ($R_5$), $R_6$ and m have the meanings reported above, $R_{10}$ can be alkyl $C_1$-$C_4$, X can be Br, I or phenylselenyl.



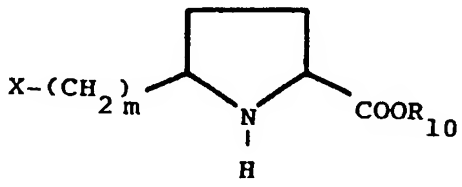
(IV) X = Br, I, Se-$C_6H_5$
(IV') X = -OH

The cyclization reaction can be carried out in the presence of radicalic initiators, such as α,α'-azabisisobutyronitrile or dibenzoyl peroxide, by addition of trialkyl- or triphenyl- tin hydrides, in aprotic apolar solvents such as ethyl ether, tetrahydrofuran, benzene, toluene, carbon tetrachloride, at temperatures generally ranging from room temperature to the solvent boiling temperature. Generally the cyclization reaction is stereoselective and among the various possible stereoisomers, a diastereoisomer mainly forms. When a mixture of stereoisomers is obtained, the single diastereoisomers can be separated and purified by means of crystallization and/or chromatographic techniques.

The compounds of general formula IV can easily be obtained starting from compounds of formula IV', wherein $R_4$ ($R_5$), $R_6$, $R_{10}$ and m have the meanings reported above and X is hydroxyl, by transformation of the alcohol into the corresponding mesylate, trifluoromethanesulfonate or

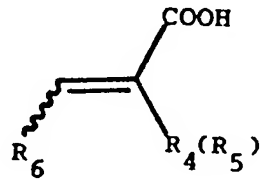
tosylate and subsequent reaction with sodium or potassium bromides or iodides, in dipolar aprotic solvents such as acetone, dimethylformamide, dimethylsulfoxide at the solvent boiling temperature. When X represents a phenylselenyl group, the transformation can be carried out starting from the corresponding alcohol, by treatment with phenylselenophthalimide, in the presence of tributyl phosphine, in solvents such as tetrahydrofuran or dichloromethane at temperatures ranging from 0°C to room temperature.

The intermediates of general formula IV' can be obtained starting from intermediates of general formula III, the preparation of which is described in literature, (see for example, J. Am. Chem. Soc., 1984, 106, 4439-4547), wherein X, $R_{10}$ and m have the meanings reported above



(III)

by coupling with compounds of general formula II, wherein $R_4$ ($R_5$) and $R_6$ have the meanings reported above.



(II)

The condensation reaction can be carried out in the presence of condensing agents, for example

dicyclohexylcarbodiimide, in aprotic apolar solvents such as tetrahydrofuran or dichloromethane, at temperatures ranging from 0°C to room temperature.

Intermediates of general formula II, wherein $R_6$ has the meanings reported above and $R_4$ ($R_5$) can be an acetylamino, t-butoxycarbonylamino or benzyloxycarbonylamino group, are generally commercially available or easily obtainable starting from the corresponding amino acids, according to what described in literature (see for example Kolar A. J. et al, Synthesis, 1977, 457-459 and Ranganathan D. et al., J. Chem. Soc. Chem. Commun., 1992, (16), 1145-1147).

The compounds described in the present invention act as thrombin inhibitors. In order to characterize and evaluate the efficacy thereof, an in vitro test for the inhibition of human thrombin (in the presence of tosyl-glycyl-prolyl-arginine-4-nitroaniline acetate as substrate) has been selected (Lottemberg et al., Methods in Enzymology, 1981, (80), 341-361).

The compounds of the invention proved to be active in the above test, showing $IC_{50}$ values lower than 5 μM. The compounds of the invention can therefore be used as active principles of pharmaceutical compositions with antithrombotic activity. The compositions of the invention can be prepared according to conventional techniques and excipients, and will contain typically 1 to 1000 mg of compounds I, and will be administered 1 to 4 times a day through the oral, parenteral, transdermal routes or any other convenient administration route.

For example, compound (3S,6S,9aS)-$N^a$-[[6-[[(3-methyl-1,2,3,4-tetrahydroquinolin-8-yl)sulfonyl]amino]-

octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldheyde hydrochloride (example 8p) showed to have an $IC_{50}$ value of 0.018 μM. Another compound, (3S,6R*,8aS)-$N^{\alpha}$-[[6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl-L-arginine aldehyde hydrochloride (example 8g) proved to have an $IC_{50}$ value of 4.60 μM.

The following examples further illustrate the invention, without limiting it.

Melting points are not corrected, the identity of the compounds and their purity have been determined by elementary analysis (C, H, N), NMR, IR and mass spectroscopies.

Example 1

(2S,5R)-1-[2-(acetylamino)propenoyl]-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)pyrrolidine

A solution of (2S,5R)-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)-pyrrolidine (10 g, 46.5 mmoles) in 150 ml of anhydrous THF is added with DCC (14.4 g, 70 mmoles). When dissolution has been completed, 2-acetylamino-acrylic acid is added (6 g, 46.5 mmoles) and stirring for 18 h at room temperature. The solution is diluted with $Et_2O$ to decrease the solubility of the formed urea, then it is filtered and concentrated to dryness. After purification by flash chromatography (AcOEt-MeOH 85:15), 12.1 g of the product are obtained, as a yellow spongy solid (80% yield).

$^1$H-NMR ($CDCl_3$)

δ: 1.44 (9H, s), 1.51-2.45 (6H, m), 2.00 (3H, s); 3.65 (3H, m), 4.45 (1H, m), 4.65 (1H, m), 4.82 (1H, s), 5.32 (1H, s), 8.5 (1H, s)

$^{13}$C-NMR ($CDCl_3$)

δ: 23.78, 28.49, 30.35, 30.70, 38.91, 55.82, 59.97, 64.72, 82.73, 104.75, 169.93.

Analogously are prepared:

a) (2S,5R)-1-[2-(acetylamino)-3-phenylpropenoyl]-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)pyrrolidine,

$^1$H-NMR ($CDCl_3$)

δ: 1.28 (9H, s), 1.6-2.50 (6H, m), 2.1 (3H, s), 3.55 (2H, m), 3.9 (1H, m), 4.5 (1H, m), 4.9 (1H, dd), 5.9 (1H, s), 7.2-7.6 (5H, m), 8.5 (1H, s)

$^{13}$C-NMR ($CDCl_3$)

δ: 22.36, 27.65, 29.52, 30.31, 38.37, 54.59, 59.15, 64.78, 81.70, 120.44, 128.31, 128.47, 128.80, 129.72, 129.76, 133.25, 170.25, 171.38, 172.01.

b) (2S,5R)-1-[2-(acetylamino)-2-butenoyl]-2-t-butoxy-carbonyl-5-(2-hydroxyethyl)pyrrolidine

$^1$H-NMR ($CDCl_3$)

δ: 1.5 (9H, s), 1.65 (3H, d), 1.6-2.4 (6H, m), 3.65 (2H, m), 4.51 (1H, s), 4.85 (1H, dd), 4.52 (1H, q), 8.52 (1H, s)

$^{13}$C-MNR ($CDCl_3$)

δ: 11.76, 21.94, 27.73, 29.49, 30.08, 38.21, 54.49, 59.07, 64.69, 81.60, 118.45, 131.57, 170.11, 171.54, 172.20.

c) (2S,5R)-1-[2-(acetylamino)-3-phenylpropenoyl]-2-t-butoxycarbonyl-5-(hydroxymethyl)pyrrolidine,

d) (2S,5R)-1-[2-(acetylamino)-2-butenoyl]-2-t-butoxy-carbonyl-5(hydroxymethyl)pyrrolidine,

e) (2S,5R)-1-[2-(acetylamino)propenoyl]-2-t-butoxycarbonyl-5-(hydroxymethyl)pyrrolidine,

f) (2S,5R)-2-[(t-butoxycarbonyl)amino]-5-(2-hydroxyethyl)-1-(3-phenylpropenoyl)pyrrolidine,

g) (2S,5R)-1-[2-[(benzyloxycarbonyl)amino]propenoyl]-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)-pyrrolidine,

$^1$H-NMR ($CDCl_3$): 1.25-2.15 (m, 6H); 1.52 (S, 9H); 3.47 (m, 2H); 4.20 (m, 2H); 5.05 (m, 2H); 5.66 (S; 1H); 7.20-7.40 (m, 6H),

h) (2S,5R)-1-[2-[(benzyloxycarbonyl)amino]-3-phenylpropenoyl]-2(tbutoxycarbonyl)-5-(2-hydroxyethyl)-pyrrolidine,

i) (2S,5R)-1-[2-[(benzyloxycarbonyl)amino]-3-(thiophen-2-yl)propenoyl]-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)pyrrolidine,

l) (2S,5R)-1-(3-phenylpropenoyl)-2-(t-butoxycarbonyl)-5-(2hydroxyethyl)-pyrrolidine,

$^1$H-NMR ($CDCl_3$): 1.47 (S, 9H); 1.55-2.51 (m, 6H); 3.71 (m, 2H); 4.50 (t, 1H); 4.75 (m, 2H); 6.59 (d, 1H); 7.30-7.60 (m, 5H); 7.70 (d, 1H).

m) (2S,5R)-1-[2-[(benzylsulfonyl)amino]-propenoyl]-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)-pyrrolidine,

n) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[[[(naphthalen-1-yl)methyl]sulfonyl]amino]propenoyl]-5-(2-hydroxyethyl)-pyrrolidine,

o) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[[(3-methylquinolin-8-yl)sulfonyl]amino]propenoyl]-5-(2-hydroxyethyl)-pyrrolidine,

p) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[[[(naphthalen-2-yl)methyl]sulfonyl]amino]propenoyl]-5-(2-hydroxyethyl)-pyrrolidine,

q) (2S,5R)-2-(t-butoxycarbonyl)-1-(3-phenylpropenoyl)-5-(3-hydroxypropyl)-pyrrolidine.

Example 2

(2S,5R)-1-[2-(acetylamino)propenoyl]-2-(t-butoxycarbonyl)5-[2-(phenylselenyl)ethyl]pyrrolidine

A solution of (2S,5R)-1-[2-(acetylamino)propenoyl]-2-(tbutoxycarbonyl)-5-(2-hydroxyethyl)-pyrrolidine (3.5 g, 10.8 mmoles) in 50 ml of anhydrous THF under $N_2$ atmosphere and at 0°C, is added with tributyl phosphine (4.4 g, 21.6 mmoles) and N-phenylselenophthalimide (6.5 g, 21.6 mmoles). The mixture is stirred for 2h at 0°C, after that solvent is removed under reduced pressure and the residue is purified by flash chromatography (EtOAc-hexane 6:4). 3.2 g of product are obtained, as a slightly yellow solid (54% yield).

$^1$H-NMR ($CDCl_3$)

δ: 1.46 (9H, s), 2.06 (3H, s), 1.5-2.28 (5H, m), 2.09-2.51 (1H, m), 2.8-3.1 (2H, m), 4.12-4.4 (1H, m), 4.61 (1H, m), 4.83 (1H, s), 5.51 (1H, s), 7.07-7.63 (5H, m), 8.42 (1H, s)

$^{13}$C-NMR ($CDCl_3$)

δ: 23.12, 24.13, 27.79, 29.20, 39.76, 58.78, 63.56, 81.65, 103.79, 126.61, 128.90, 132.291, 137.35, 169.34, 171.63.

MS ($FAB^+$): m/e 467 ($MH^+$)

Analogously are prepared:

a) (2S,5R)-1-[2-(acetylamino)-3-phenylpropenoyl]-2-t-butoxycarbonyl-5-[2-(phenylselenyl)ethyl]pyrrolidine

$^1$H-NMR ($CDCl_3$)

δ: 1.21 (9H, s), 2.15 (3H, s), 1.1-2.4 (6H, m), 2.89 (2H, m), 4.22 (1H, m), 4.85 (1H, d), 5.61 (1H, s), 7.0-7.6 (10H, m), 10.25 (1H, s)

$^{13}$C-NMR ($CDCl_3$)

δ: 22.27, 24.27, 27.70, 29.45, 29.79, 34.63, 58.24, 64.23, 81.28, 121.08, 126.51, 128.29, 128.41, 128.67, 128.91, 130.31, 132.11, 133.38, 170.25, 170.65, 171.80

b) (2S,5R)-1-[2-(acetylamino)-2-butenoyl]-2-t-butoxycarbonyl-5-[2-(phenylselenyl)ethyl]pyrrolidine,

$^{1}$H-NMR ($CDCl_3$)

δ: 1.52 (9H, s), 2.33 (3H, s), 1.2-2.51 (9H, m), 2.95 (2H, m), 4.33 (1H, m), 4.82 (1H, m), 5.23 (1H, q), 7.1-7.60 (5H, m), 9.65 (1H, s)

$^{13}$C-NMR ($CDCl_3$)

δ: 11.91, 22.33, 24.33, 27.84, 29.48, 35.99, 58.04, 63.26, 81.31, 118.908, 126.51, 128.85, 132.41

c) (2S,5R)-1-[2-(acetylamino)-3-phenylpropenoyl]-2-t-butoxycarbonyl-5-[(phenylselenyl)methyl]pyrrolidine,

d) (2S,5R)-1-[2-(acetylamino)2-butenoyl]-2-t-butoxycarbonyl-5-[(phenylselenyl)methyl]pyrrolidine,

e) (2S,5R)-1-[2-(acetylamino)-propenoyl]-2-t-butoxycarbonyll-5[(phenylselenyl)methyl]pyrrolidine,

f) (2S,5R)-1-[2-[(benzyloxycarbonyl)amino]propenoyl]-2-(t-butoxycarbonyl)-5-[2-(phenylselenyl)ethyl]-pyrrolidine,

g) (2S,5R)-1-[2-[(benzyloxycarbonyl)amino]-3-(thiophen-2-yl)propenoyl]-2-(t-butoxycarbonyl)-5-[2-(phenylselenyl)ethyl]pyrrolidine,

h) (2S,5R)-2-(t-butoxycarbonyl)-5-[2-(phenylselenyl)ethyl]-1-(3-phenylpropenoyl)-pyrrolidine,

$^{1}$H-NMR ($CDCl_3$): 1.47 (S, 9H); 1.70-2.50 (m, 6H); 2.90-3.15 (m, 2H); 4.31-4.52 (m, 2H); 6.85 (d, 1H); 7.10-7.80 (m, 11H)

i) (2S,5R)-2-(t-butoxycarbonyl)-5-[2-(phenylselenyl)-ethyl]-1-[3(thiophen-2-yl)propenoyl]-pyrrolidine,

l) (2S,5R)-2-(t-butoxycarbonyl)-5-[3-(phenylselenyl)-propyl]-1-(3-phenylpropenoyl)-pyrrolidine.

Example 3

(2S,5R)-1-[2-(acetylamino)propenoyl]2-(t-butoxycarbonyl)-5-(2-iodoethyl)-pyrrolidine

A solution of (2S,5R)-1-[2-(acetylamino)propenoyl]-2-(t-butoxycarbonyl)-5-(2-hydroxyethyl)pyrrolidine (10.3 g, 31.5 mmoles) in 200 ml of anhydrous $CH_2Cl_2$, under $N_2$ atmosphere and cooled at 0°C, is added with the triethylamine (6.1 ml, 44.1 mmoles) and subsequently a solution of methanesulfonyl chloride (3.1 ml, 39.7 mmoles) in 70 ml of $CH_2Cl_2$. The mixture is stirred 0°C until the starting product disappears, then it is washed repeatedly with water, dried over $Na_2SO_4$ and solvent is removed under reduced pressure. The resulting crude mesylate is redissolved in 300 ml of acetone , the solution is added with sodium iodide (22.8 g, 150 mmoles), finally it is refluxed and after 3 h the solvent is removed under reduced pressure. The residue is redissolved in $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$) and concentrated to dryness. After purification by flash chromatography (EtOAc- MeOH 95:5), 11.0 g of a slightly yellow solid are obtained.

(80% yield)

m.p. 48-50°C (dec)

$^1$H-NMR ($CDCl_3$): 1.45 (S, 9H); 1.52-2.15 (m, 8H); 2.08 (S, 3H); 3.27 (m, 2H); 4.28 (m, 1H) 4.53 (S, 1H); 4.89 (S, 1H); 5.76 (S, 1H); 7.90 (S, 1H)

Analogously are prepared:

a) (2S,5R)-2-(t-butoxycarbonyl)-5-(2-iodoethyl)-1-(3-phenylpropenoyl)-pyrrolidine,

b) (2S,5R)-2-(t-butoxycarbonyl)-5-(2-iodoethyl)-1-[3-(thiophen-2-yl)propenoyl]-pyrrolidine,

c) (2S,5R)-2-(t-butoxycarbonyl)-5-(2-bromomethyl)-1-[-2-(acetylamino)propenoyl]-pyrrolidine,

d) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[(benzyloxycarbonyl)amino]propenoyl]-5-(2-iodoethyl)-pyrrolidine,

$^1$H-NMR ($CDCl_3$): 1.33 (s, 9H); 1.30-2.20 (m, 4H); 2.80-3.20 (m, 4H); 4.12 (m, 1H); 4,22 (m, 1H); 4.80 (s, 1H); 4.86 (s, 2H); 5.72 (s, 1H); 6.90 (s, 1H); 7.35 (m, 5H).

e) (2S,5R)-2-(t-butoxycarbonyl)-1-(2-butenoyl)-5-(2-iodoethyl)-pyrrolidine,

f) (2S,5R)-1-[2-[(benzylsulfonyl)amino]-propenoyl]-2-(t-butoxycarbonyl)-5-(2-iodoethyl)-pyrrolidine,

g) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[[[(naphthalen-1-yl)methyl]sulfonyl]amino]propenoyl]-5-(iodoethyl)-pyrrolidine,

h) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[[(3-methylquinolin-8-yl)sulfonyl]amino]propenoyl]-5-(2-iodoethyl)-pyrrolidine,

i) (2S,5R)-2-(t-butoxycarbonyl)-1-[2-[[[(naphthalen-2-yl)methyl]sulfonyl]amino]propenoyl]-5-(2-iodoethyl)-pyrrolidine.

Example 4

(3S,6S,9aS)-6-acetylamino-3-(t-butoxycarbonyl)-octahydropyrrolo[1,2-a]azepin-5-one

A solution of (2S,5R)-2-(t-butoxycarbonyl)-5-(2-iodoethyl)-1-[2-(acetylamino)propenoyl]-pyrrolidine (8.5 g, 19.5 mmoles) in 1500 ml of anhydrous benzene under reflux and $N_2$ atmosphere, is added drop by drop during 6

h with a solution of $Bu_3SnH$ (6.5 ml, 23.1 mmoles) and AIBN (0.65 g, 3.9 mmoles) in 350 ml of benzene.

When the reaction is complete, the mixture is cooled at room temperature, the volume is reduced to about 300 ml and KF saturated solution is added. Stirring is continued for 8 h, salts are filtered off through celite, the phases are separated and the organic phase is dried over $Na_2SO_4$. Upon removal of the solvent under reduced pressure and purification by flash chromatography (EtOAc-MeOH 95:5) 3.7 g of a white foamy solid are obtained (62% yield).

$^1$H-NMR ($CDCl_3$)

δ: 1.46 (9H, s), 1.97 (3H, s), 1.50-2.29 (10H, m), 3.78-3.88 (1H, m), 4.43 (1H, m), 4.50 (1H, dd), 6.94 (1H, d)

$^{13}$C-NMR ($CDCl_3$)

δ: 23.29, 27.95, 27.49, 27.69, 31.14, 32.83, 34.21, 53.24, 59.15, 61.33, 81.48, 169.13, 170.05.

MS (EI): m/e 310

Analogously are prepared:

a) (3S,6S,7R,9aS)-6-(acetylamino)-3-(t-butoxycarbonyl)7-methyloctahydropyrrolo[1,2-a]azepin-5-one,

$^1$H-NMR ($CDCl_3$)

δ: 1.50 (9H, s), 1.50-2.52 (7H, m), 3.83 (1H, m), 4.41-4.63 (1H, m), 4.61 (1H, m), 7.12 (1H, db).

b) (3S,6R,8aR)-6-(acetylamino)-6-(benzyl)-3-(t-butoxycarbonyl)-octahydroindolizin-5-one,

$^1$H-NMR ($CDCl_3$),

δ: 1.46 (9H, s), 2.0 (3H, s), 1.5-2.1 (6H, m), 2.32 (1H, m), 2.72 (1H, m), 3.1 (1H, m), 3.32 (1H, d), 3.42 (1H, d), 4.25 (1H, m), 6.55 (1H, s), 7.0-7.4 (5H, m)

$^{13}$C-NMR ($CDCl_3$)

δ: 24.27, 26.98, 27.75, 27.75, 27.84, 28.16, 30.21, 31.54, 42.18, 58.40, 60.04, 77.43, 126.63, 127.63, 127.28, 127.79, 127.91, 128.22, 130.24.

c) (3S,6R*,7aR)-6-acetylamino-6-benzyl-3-(t-butoxycarbonyl)-hexahydropyrrolizin-5-one,

d) (3S,6R*,7aR)-6-acetylamino-6-ethyl-3-(t-butoxycarbonyl)-hexahydropyrrolizin-5-one,

e) (3S,6R*,7aR)-6-acetylamino-6-methyl-3-(t-butoxycarbonyl)-hexahydropyrrolizin-5-one,

f) (3S,6R*,7R*,8aR)-6-acetylamino-7-phenyl-3-(t-butoxycarbonyl)-octahydroindolizin-5-one,

g) (3S,6R*,7R*,8aR)-6-acetylamino-7-methyl-3-(t-butoxycarbonyl)-octahydroindolizin-5-one,

h) (3S,6R*,8aR)-6-acetylamino-3-(t-butoxycarbonyl)-octahydroindolizin-5-one,

i) (3S,6R*,8aR)-6-benzyl-3-(t-butoxycarbonyl)octahydroindolizin-5-one,

l) (3S,6R*,8aR)-3-(t-butoxycarbonyl)-6-[(thiophen-2-yl)methyl]-octahydroindolizin-5-one,

m) (3S,6R*,8aR)-6-[(benzyloxycarbonyl)amino]-3-(t-butoxycarbonyl)-6-[(thiophen-2-yl)methyl]-octahydroindolizin-5-one,

n) (3S,6S,9aS)-3-(t-butoxycarbonyl)-6-[(benzylsulfonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one,

o) (3S,6S,9aS)-3-(t-butoxycarbonyl)-6-[(benzyloxycarbonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one,

$^1$H-NMR ($CDCl_3$) δ: 1.53 (s, 9H); 1.50-2.45 (m, 10H); 3.80 q, 1H); 4.20 (m, 1H); 4.55 (t, 1H); 5.09 (s, 2H); 6.21 (m, 1H); 7.35 (m, 5H).

p) (3S,6S,9aS)-3-(t-butoxycarbonyl)-6[[[(naphthalen-1-yl)methyl]sulfonyl]amino]-octahydropyrrolo[1,2-

a]azepin-5-one,

q) (3S,6S,9aS)-3-(t-butoxycarbonyl)-6-[[(3-methylquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one.

Example 5

(3S,6S,9aS)-6-acetylamino-octahydropyrrolo-[1,2-a]azepin-5-one-3-carboxylic acid

A solution of (3S,6S,9aS)-3-(t-butoxycarbonyl)-6-acetylamino-octahydropyrrolo[1,2-a]azepin-5-one (0.88 g, 2.9 mmoles) in 10 ml of anhydrous $CH_2Cl_2$ at room temperature, is added with 10 ml of $CF_3COOH$. The mixture is stirred until the starting tert-butyl ester disappears and the solvent is removed under reduced pressure. The residue is redissolved in $CH_2Cl_2$ and extracted with 2M $Na_2CO_3$. The alkali aqueous phase is acidified to pH = 2 with 2N HCl and the solvent is evaporated under reduced pressure.

The crude acid is purified by chromatography on a ion exchange resin (DOWEX) eluting with 2N HCl. Upon removing the solvent under reduced pressure and drying, 0.48 g of a white solid are obtained (67% yield).

$^1$H-NMR ($CDCl_3$): 0.95-2.43 (m, 10H); 1.99 (S, 3H); 3.84 (m, 1H); 4.51 (m, 1H); 4.63 (m, 1H); 7.05 (d, 1H).

Analogously are prepared:

a) (3S,6R,8aR)-6-acetylamino-6-benzyl-octahydroindolizin-5-one-3-carboxylic acid,

m.p. 170-174°C (dec)

$^1$H-NMR ($CDCl_3$): 1.35-2.20 (m, 7H); 2.09 (S, 3H); 2.80 (m, 1H); 3.47 (AB syst., 2H); 4.07 (m, 1H); 4.51 (m, 1H); 7.10-7.25 (m, 5H)

b) (3S,6R*,8aS)-6-benzyl-octahydroindolizin-5-one-3-

carboxylic acid,

$^1$H-NMR ($CDCl_3$) δ: 0.95-2.45 (m, 7H); 2.81 (m, 2H); 3.45 (m, 2H); 4.51 (d, 1H); 7.45 (m, 5H),

c) (3S,6R*,7R*,9aS)-6-acetylamino-7-methyl-octahydropyrrolo[1,2-a]azepin5-one-3-carboxylic acid,

d) (3S,6R*,8aR)-6-acetylamino-octahydroindolizin-5-one-3-carboxylic acid,

e) (3S,6S,9aS)-6-[(benzyloxycarbonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-carboxylic acid,

f) 6-[(thiophen-2-yl)methyl]-octahydroindolizin-5-one-3-carboxylic acid,

g) (3S,6S,9aS)-6-[[(naphthalen-1-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]-azepin-5-one-3-carboxylic acid,

m.p. 192-197°C,

h) (3S,6S,9aS)-6-[[(naphthalen-2-yl)sulfonyl]amino]-octahydropyrrolo[1,2a]azepin-5-one-3-carboxylic acid,

i) (3S,6R*,7R*,8aR)-6-methylamino-7-phenyl-octahydroindolizin-5-one-3-carboxylic acid,

l) (3S,6S,9aS)-6-[[(benzyl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-carboxylic acid,

$^1$H-NMR ($CDCl_3$) δ: 1.15-2.37 (m, 10H); 3.17-3.52 (m, 2H); 4.12-4.48 (m, 2H); 4.57 (m, 1H); 5.87 (d, 1H); 7.37 (m, 5H),

m) (3S,6S,9aS)-6-[[(3-methylquinolin-8-yl)sulfonyl]-amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-carboxylic acid,

m.p. 228-232°C,

n) (3S,6S,9aS)-6-[[[(naphthalen-1-yl)methyl]sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-

carboxylic acid,

o) (3S,6R*,9aS)-6-benzyl-octahydropyrrolo-[1,2-a]-azepin-5-one-3-carboxylic acid,

m.p. 105-110°C (dec.).

Example 6

(3S,6S,9aS)-$N^{a}$-[(6-acetylamino-octahydropyrrolo[1,2-a]-azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam

A solution of (3S,6S,9aS)-6-(acetylamino)-octahydropyrrolo[1,2-a]azepin-5-one-3-carboxylic acid (0.41 g, 1.62 mmoles) in 10 ml of anhydrous DMF under $N_2$ atmosphere and cooled at -15°C is added with a syringe with, in turn, N-methylmorpholine (0.18 ml, 1.62 mmoles) and isobutyl chloroformate (0.23 ml, 1.62 mmoles). The reaction mixture is stirred for 30 min a -15°C, after that a solution of N-methylmorpholine (0.36 ml, 3,24 mmoles) and $N^{W}$-benzyloxycarbonyl-L-arginine lactam hydrochloride (0.6 g, 1.62 mmoles) dissolved in 10 ml of DMF is added.

The resulting suspension is stirred for 2 h, left to warm at room temperature and finally the solvent is removed under reduced pressure. The residue is taken up with $CH_2Cl_2$, washed with water and with a NaCl saturated solution, dried ($Na_2SO_4$) and the solvent is removed under reduced pressure. After purification by flash chromatography ($CH_2Cl_2$-MeOH 95:5) and grinding with $Et_2O$-hexane, 0.63 g of product are obtained, as a white amorphous solid (54% yield).

m.p. 145-150°C (dec); $^1$H-NMR ($CDCl_3$): 0.95 (d, 1H); 1.20-2.50 (m, 13H); 2.05 (S, 3H); 3.49 (m, 1H); 3.80 (m, 1H); 4.57 (m, 2H); 4.70 (d, 1H); 4.91 (m, 1H);

5.14/5.2H); 6.89 (d, 1H); 7.20-7.50 (m, 10H); 7.63 (d, 1H); 9.50 (m, 2H); MS ($FAB^+$): m/z 527.

Analogously are prepared:

a) (3S,6R,8aR)-$N^{\alpha}$-[(6-acetylamino-6-benzyl-octahydro-indolizin-5-one-3-yl)carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

m.p. 121-125°C (dec); $^1H$-NMR ($CDCl_3$): 0.95 (d, 1H); 1.20-2.35 (m, 13H); 2.04 (S, 3H); 3.70 (m, 2H); 4.40-4.73 (m, 3H); 5.12 (S, 2H); 6.25 (d, 1H); 7.05-7.41 (m, 10H); 7.80 (d, 1H); 9.20-9.50 (m, 2H)

MS ($FAB^+$): m/z 603

b) -$N^{\alpha}$-[[(6-acetamido-7-methyloctahydro[1,2-a]azepin-5one3yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

c) -$N^{\alpha}$-[[6-acetamido-6-benzyl-hexahydropyrrolizin-5-one3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

d) -$N^{\alpha}$-[[6-acetamido-6-benzyl-hexahydropyrrolizin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

e) -$N^{\alpha}$-[[6-acetamido-6-ethyl-hexahydropyrrolizin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

f) -$N^{\alpha}$-[[6-acetamido-6-methyl-hexahydropyrrolizin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

g) (3S,6S,9aS)-$N^{\alpha}$-[[6-[[(3-methylquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

m.p. 205-210°C (dec.),

h) (3S,6S,9aS)-$N^{\alpha}$-[[6-[[[(naphthalen-1-yl)methyl]sulfonyl]amino]-octahydro-pyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

i) (3S,6S,9aS)-$N^{\alpha}$-[[6-[(benzylsulfonyl)amino]-octahydro-pyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

m.p. 88-95°C (dec.),

l) (3S,6S,9aS)-$N^{\alpha}$-[[6-[[(naphthalen-1-yl)sulfonyl]amino]-octahydro-pyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

m.p. 130-135°C (dec.)

m) (3S,6R*,9aS)-$N^{\alpha}$-[[6-benzyl-octahydropyrrolo[1,2-a]-azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

$^{1}$H-NMR ($CDCl_3$) δ: 0.95-2.50 (m, 13H); 2.83-3.52 (m, 5H); 4.02 (m, 1H); 4.43-4.95 (m, 3H), 5.14 (s, 2H); 7.15-7.50 (m, 10H); 7.80 (d, 1H); 9.50 (m, 2H),

n) (3S,6R*,9aS)-$N^{\alpha}$-[[6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl-$N^{W}$-benzyloxycarbonyl-L-arginine lactam,

$^{1}$H-NMR ($CDCl_3$) δ: 1.40-2.20 (m, 8H); 2.50-2.83 (m, 4H); 3.21-3.52 (m, 4H); 4.37 (d, 1H); 4.64 (m, 1H); 4.86 (m, 1H); 5.14 (s, 2H); 6.94 (d, 1H); 7.20-7.48 (m, 10H); 9.50 (m, 2H).

Example 7

(3S,6S,9aS)-$N^{\alpha}$-[[(6-acetylamino-octahydropyrrolo[1,2-a]-azepin-5-one)-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde

A solution of (3S,6S,9aS)-$N^{\alpha}$-[[(6-acetylamino-octahydropyrrolo[1,2-a]azepin-5-one)-3-yl]carbonyl]-$N^{W}$-ben-

zyloxycarbonyl-L-arginine aldehyde lactam (0.2 g, 0.38 mmoles) in 5 ml of anhydrous THF, cooled at -20°C and under $N_2$ atmosphere, is added drop by drop with a suspension of $LiAlH_4$ (0.010 g, 0.23 mmoles) in 4 ml of anhydrous THF. After 2 h stirring at -20°C, 1N HCl is added to pH 7. The mixture is left to warm at room temperature and the suspension is filtered through $Na_2SO_4$. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography ($CH_2Cl_2$-MeOH 95:5). 0.18 g of a white amorphous solid are obtained (92% yield).

$^1$H-NMR ($CDCl_3$): 0.88 (d, 1H); 1.20-2.25 (m, 16H); 2,05 (S, 3H); 3.10 (m, 1H); 3.50 (m, 1H); 3.82 (m, 1H); 4.40-4.75 (m, 3H); 5.09 (S, 2H); 5.82 (s, 1H); 6.82 (d, 1H); 7.37 (m, 5H); MS ($FAB^+$): m/z 529 ($MH^+$)

Analogously are prepared:

a) (3S,6R,8aR)-$N^a$-[[(6-acetylamino-6-benzyl-octahydro-indolizin-5-one)3-yl]carbonyl]-$N^w$-benzyloxycarbonyl-L-arginine aldehyde

m.p. 95-100°C (dec); $^1$H-NMR ($CDCl_3$): 0.7 (m, 2H); 1.20-2.10 (m, 14H); 2.10 (S, 3H); 3.05-3.20 (m, 2H); 3.70-4.30 (m, 3H); 5.05 (S; 2H); 5.51 (m, 1H); 6.27 (d, 1H); 7.15-7.49 (m, 10H); MS ($FAB^+$): m/z 605 ($MH^+$).

b) (3S,6R*,7R*,9aS)-$N^a$-[[(6-acetylamino-7-methyloctahydro[1,2-a]azepin-5-one)-3-yl]carbonyl]-$N^w$-benzyloxycarbonyl-L-arginine aldehyde,

c) -$N^a$-[[(6-acetylamino)-6-benzyl-hexahydropyrrolizin-5-one)-3-yl]carbonyl]-$N^w$-benzyloxycarbonyl-L-arginine aldehyde,

d) -$N^a$-[[(6-acetylamino-6-ethylhexahydropyrrolizin-5-one)-3-yl]carbonyl]-$N^w$-benzyloxycarbonyl-L-arginine

aldehyde,

e) -$N^{\alpha}$-[[(6-acetylamino-6-methylhexahydropyrrolizin-5-one)-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

f) (3S,6R*,7R*,8aR)-$N^{\alpha}$-[[(6-amino-7-phenyl-octahydroindolizin-5-one)-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

g) (3S,6R*,8aS)-$N^{\alpha}$-[[6-benzyl-octahydroindolizin-5-one)-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

m.p. 105-113°C (dec.),

h) (3S,6S,9aS)-$N^{\alpha}$-[[[6-[(benzylsulfonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one]3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

i) (3S,6S,9aS)-$N^{\alpha}$-[[[6-[(-1-naphthylsulfonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one]-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

l) (3S,6S,9aS)-$N^{\alpha}$-[[[6-[(2-naphthylsulfonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one]-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

m) (3S,6S,9aS)-$N^{\alpha}$-[[[6-[[(1-naphthylmethyl)sulfonyl]-amino]octahydropyrrolo[1,2-a]-azepin-5-one]-3-yl]-carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

n) (3S,6S,9aS)-$N^{\alpha}$-[[6-[[(3-methylquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde,

m.p. 98-110°C (dec),

o) (3S,6R*,9aS)-$N^{\alpha}$-[[6-benzyl-octahydropyrrolo[1,2-a]-azepin-5-one-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde.

Example 8

(3S,6S,9aS)-$N^{\alpha}$-[[[6-acetylamino-octahydropyrrolo[1,2-a]-azepin-5-one]-3-yl]carbonyl]-L-arginine aldehyde hydrochloride

A solution of (3S,6S,9aS)-$N^{\alpha}$-[[(6-acetylamino-octahydropyrrolo[1,2-a]azepin-5-one]-3-yl]carbonyl]-$N^{W}$-benzyloxycarbonyl-L-arginine aldehyde (0.18 g, 0.34 mmoles) in 10 ml of THF is added with palladium on charcoal (10%, 35 mg) and 0.35 ml of 1N HCl. The mixture is placed under hydrogen atmosphere and left to react under stirring until the starting product disappears, then it is filtered through Celite and the solvent is removed under reduced pressure. Upon grinding with $Et_2O$, 0.13 g of a white amorphous solid are obtained (88% yield).

m.p. 125-135°C (dec); $^1$H-NMR (DMSO-$d_6$): 0.95 (m, 1H); 1.30-2.20 (m, 13H); 2.07 (S, 3H); 3.07-3.42 (m, 3H); 3.82 (m, 2H); 4.50 (m, 2H); 7.03 (m, 1H); 7.51-7.85 (m, 4H); 9.45 (S, 1H); MS (FAB$^+$): m/z 395 ($MH^+$).

Analogously are prepared:

a) (3S,6R,8aR)-$N^{\alpha}$-[[(6-acetylamino-6-benzyloctahydro-indolizin-5-one)-3-yl]carbonyl]-L-arginine aldehyde hydrochloride

m.p. 148-152°C (dec); $^1$H-NMR (DMSO-$d_6$): 0.71-1.05 (m, 2H); 1.25-2.30 (m, 12H); 2.07 (S, 3H); 3.20-3.48 (m, 2H); 3.60-3.75 (m, 1H); 4.05-4.46 (m, 3H); 6.51 (S, 1H); 7.05-7.20 (m, 5H); 7.58 (m, 4H); 9.52 (S, 1H)

MS (FAB$^+$): m/z 471 ($MH^+$).

b) (3S,6R*,7R*,9aS)-$N^{\alpha}$-[[(6-acetylamino-7-methyloctahydropyrrolo[1,2-a]azepin-5-one)-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

c) (3S,6R*,7aR)-$N^{\alpha}$-[[(6-acetylamino-6-benzyl-hexahy-

dropyrrolizin-5-one)3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

d) (3S,6R*,7aR)-N$^{\alpha}$-[[(6-acetylamino-6-ethylhexahydropyrrolizin-5-one)3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

e) (3S,6R*,7aR)-N$^{\alpha}$-[[(6-acetylamino-6-methylhexahydropyrrolizin-5-one)-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

f) (3S,6R*,7R*,8aR)-N$^{\alpha}$-[[(6-amino-7-phenyl-octahydroindolizin-5-one)-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

g) (3S,6R*,8aS)-N$^{\alpha}$-[[(6-benzyl-octahydroindolizin-5-one)3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

m.p. 115-122°C (dec.); MS (FAB$^+$): m/z 414 (MH$^+$)

h) (3S,6S,9aS)-N$^{\alpha}$-[[[6-[(benzylsulfonyl)amino]-octahydropyrrolo[1,2a]azepin-5-one]3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

m.p. 95-110°C (dec.); MS (FAB$^+$): m/z 507 (MH$^+$)

i) (3S,6S,9aS)-N$^{\alpha}$-[[[6-[(1-naphthylsulfonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one]-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

m.p. 103-107°C (dec.); MS (FAB$^+$): m/z 543 (MH$^+$)

l) (3S,6S,9aS)-N$^{\alpha}$-[[[6-[(2-naphthylsulfonyl)amino]-octahydropyrrolo[1,2-a]azepin-5-one]-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,

m) (3S,6S,9aS)-N$^{\alpha}$-[[[6-[[(1-naphthylmethyl)sulfonyl]-amino]-octahydropyrrole[1,2-a]-azepin-5-one]-3-yl]-carbonyl]-L-arginine aldehyde hydrochloride,

n) (3S,6S,9aS)-N$^{\alpha}$-[[6-[[(3-methylquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-

yl]carbonyl]-arginine aldehyde hydrochloride,
MS (FAB$^+$): m/z 558 (MH$^+$),

o) (3S,6R*,9aS)-N$^a$-[[6-benzyl-octahydropyrrolo[1,2-a]-azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,
m.p. 92-105°C (dec.); MS (FAB$^+$): m/z 428 (MH$^+$),

p) (3S,6S,9aS)-N$^a$-[[6-[[(3-methyl-1,2,3,4-tetrahydroquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde hydrochloride,
m.p. 170-175°C (dec.); MS (FAB$^+$): m/z 562 (MH$^+$).

Example 9

(3S,6S,9aS)-6-amino-3-(t-butoxycarbonyl)-octahydropyrrolo[1,2-a]azepin-5-one

A solution of (3S,6S,9aS)-6-[(benzyloxycarbonyl)-amino]-3-(t-butoxycarbonyl)-octahydropyrrolo[1,2-a]azepin-5-one (5.03 g, 12.4 mmoles) in 200 ml of MeOH, si added with palladium on charcoal (10%, 0.35 g). The mixture is placed under hydrogen atmosphere and reacted with stirring until the starting compound disappears. The suspension is filtered through celite, solvent is removed under reduced pressure and the residue is dried in a drier with $P_2O_5$ at room temperature. 2.77 g of a transparent, sticky residue are obtained (83% yield).
$^1$H-NMR ($CDCl_3$) δ: 1.47 (s, 9H); 1.50-2.31 (m, 10H); 3.42 (d, 1H); 3.75 (m, 1H); 4.52 (m, 1H).

Example 10

(3S,6S,9aS)-6-[(benzylsulfonyl)amino]-3-(t-butoxycarbonyl)-octahydropyrrolo[1,2-a]azepin-5-one

A solution of (3S,6S,9aS)-6-amino-3-(t-butoxycarbonyl)-octahydropyrrolo[1,2-a]azepin-5-one (1.2 g, 4.47

mmoles) in 30 ml of $CH_2Cl_2$ is added with triethylamine (1 ml, 5.81 mmoles), then with benzylsulfonyl chloride (1.02 g, 5.36 mmoles).

The mixture is stirred at room temperature for 4 h, washed with a 5% citric acid solution, with water, finally with a NaCl saturated solution, then it is dried over $Na_2SO_4$ and solvent is removed under reduced pressure. The resulting sticky residue is purified by flash chromatography (eluent: hexane/EtOAc 1:1).

After purification, 1.70 g of the pure product are obtained in the form of a waxy solid (89% yield).
$^1$H-NMR ($CDCl_3$) δ: 1.48 (s, 9H); 1.48-2.20 (m, 10H); 3.17 (m, 1H); 3.32 (m, 1H); 4.10-4.48 (m, 3H); 5.87 (d, 1H); 7.25-7.48 (m, 5H).

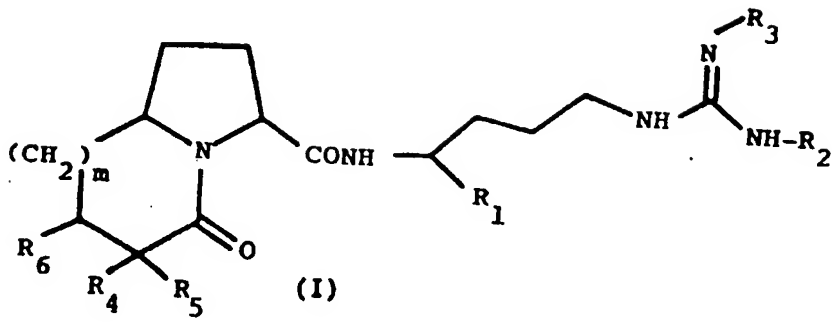
Analogously are prepared:

(3S,6S,9aS)-6-[[(naphthalen-1-yl)sulfonyl]amino]-3-(t-butoxycarbonyl)-octahydropyrrolo[1,2-a]azepin-5-one
$^1$H-NMR ($CDCl_3$) δ: 1.47 (s, 9H); 1.50-2.23 (m, 10H); 3.56 (s, 1H); 3.88 (s, 1H); 4.34 (t, 1H); 6.50 (d, 1H); 7.48-7.72 (m, 3H); 7.95 (d, 1H); 8.04 (d, 1H); 8.23 (d, 1H); 8.68 (d, 1H).

(3S,6S,9aS)-3-(t-butoxycarbonyl-6-[[(3-methylquinolin-8-yl)sulfonyl]amino]-octahydropyrrolo[1,2-a]azepin-5-one
$^1$H-NMR ($CDCl_3$) δ: 1.48 (s, 9H); 1.50-2.37 (m, 10H); 2.63 (s, 3H); 3.60 (m, 1H); 4.04 (m, 1H); 4.29 (m, 1H); 7.52 (m, 2H); 8.01 (m, 2H); 8.28 (d, 1H); 8.93 (d, 1H).

CLAIMS

1. Compounds of general formula I:

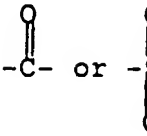
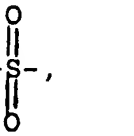


(I)

wherein:

- m is 0, 1, 2 or 3;
- $R_1$ is a group of formula -CHO, $-CH_2OH$, COOH, $-B(OH)_2$;
- $R_2$, $R_3$ are independently hydrogen, $COOR_7$, $C_1$-$C_4$ alkyl, benzyl, $-NO_2$;
- $R_4$, $R_5$ are independently hydrogen, $NR_8R_9$, straight or branched $C_1$-$C_7$ alkyl, $C_3$-$C_7$ cycloalkyl or an arylalkyl or heteroarylalkyl group, optionally substituted at the ring with one or more substituents such as halogen (Cl, Br, I), methoxyl, trifluoromethyl, straight or branched $C_1$-$C_7$ alkyl;
- $R_6$ is hydrogen, straight or branched $C_1$-$C_7$ alkyl, $C_3$-$C_7$ cycloalkyl or an aryl, heteroaryl, arylalkyl or heteroarylalkyl group, optionally substituted at the ring with one or more substituents such as halogen (Cl, Br, I), methoxy, trifluoromethyl, straight or branched $C_1$-$C_7$ alkyl;
- $R_7$ is $C_1$-$C_4$ alkyl, benzyl;
- $R_8$, $R_9$ are independently hydrogen, straight or

branched $C_1$-$C_7$ alkyl or a group of general formula -W-Q wherein:

- W can be a group  or  ,

- Q can be a phenyl, benzyl, naphthyl, quinolyl, naphthylmethyl, tetrahydroquinolyl, tetrahydroisoquinolyl group, optionally substituted with one or more groups such as halogen (Cl, Br, I), straight or branched $C_1$-$C_7$ alkyl, methoxy, trifluoromethyl, the stereoisomeric forms thereof and the salts thereof with pharmaceutically acceptable acids.

2. Compounds according to claim 1, wherein m is 2, $R_1$ is -CHO, $R_6$ is hydrogen and $R_2$, $R_3$, $R_4$, $R_5$ have the meanings reported above.

3. As compounds according to claim 2:

(3S,6S,9aS)-$N^{\alpha}$-[[6-acetylamino-octahydropyrrolo[1,2-a]-azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,9aS)-$N^{\alpha}$-[[6-methylamino-octahydropyrrolo[1,2-a]-azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,9aS)-$N^{\alpha}$-[[6-[[(naphthalen-1-yl)sulfonyl]amino]-octahydropyrolo-[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R*,9aS)-$N^{\alpha}$-[[6-benzyl-octahydropyrrolo-[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,9aS)-$N^{\alpha}$-[[6-[(benzylsulfonyl)amino]-octahydropyrrolo-[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,9aS)-$N^{\alpha}$-[[6-[[[naphthalen-1-yl)methyl]sulfonyl]-amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]L-arginine aldehyde,

(3S,6S,9aS)-N$^{\alpha}$-[[6-[[[(naphthalen-2-yl)methyl]sulfonyl]-amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,9aS)-N$^{\alpha}$-[[6-[[(3-methylquinolin-8-yl)sulfonyl]-amino]-octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,9aS)-N$^{\alpha}$-[[6-[[(3-methyl-1,2,3,4-tetrahydroquinolin-8-yl)sulfonyl]amino]octahydropyrrolo[1,2-a]azepin-5-one-3-yl]carbonyl]-L-arginine aldehyde.

4. Compounds according to claim 1, wherein m is 1, $R_1$ is -CHO and $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ have the meanings reported above.

5. As compounds according to claim 4:

(3S,6S,8aS)-N$^{\alpha}$-[[6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R,8aS)-N$^{\alpha}$-[[6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,8aS)-N$^{\alpha}$-[[6-[(thiophen-2-yl)methyl]-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R,8aS)-N$^{\alpha}$-[[(6-[(thiophen-2-yl)methyl]-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,8aS)-N$^{\alpha}$-[[6-[(naphthalen-2-yl)methyl]octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R,8aS)-N$^{\alpha}$-[[6-[(naphthalen-2-yl)methyl]octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,8aS)-N$^{\alpha}$-[[6-[(naphthalen-1-yl)methyl]-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R,8aS)-N$^{\alpha}$-[[6-[(naphthalen-1-yl)methyl]-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R,8aR)-N$^{\alpha}$-[[6-acetylamino-6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,8aR)-N$^{\alpha}$-[[6-acetylamino-6-benzyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,8aR)-N$^{\alpha}$-[[6-benzyl-6-methylamino-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R,8aR)-N$^{\alpha}$-[[(6-benzyl-6-methylamino-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6S,8aR)-N$^{\alpha}$-[[6-benzyl-6-[(t-butoxycarbonyl)amino]-octahydroindolizin-5-one]-3-yl]-L-arginine aldehyde,

(3S,6R,8aR)-N$^{\alpha}$-[[6-benzyl-6-[(t-butoxycarbonyl)amino]-octahydroindolizin-5-one]-3-yl]-L-arginine aldehyde,

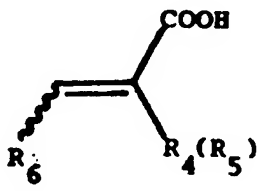
(3S,6R*,7R*,8aR)-N$^{\alpha}$-[[6-amino-7-phenyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R*,7R*,8aR)-N$^{\alpha}$-[[6-(methylamino)-7-phenyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

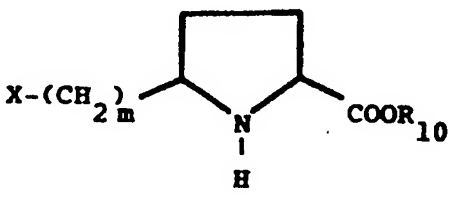
(3S,6R*,7R*,8aR)-N$^{\alpha}$-[[6-(acetylamino)-7-phenyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde,

(3S,6R*,7R*,8aR)-N$^{\alpha}$-[[6-(acetylamino)-7-methyl-octahydroindolizin-5-one-3-yl]carbonyl]-L-arginine aldehyde.

6. A process for the preparation of the compounds of general formula I, which comprises the condensation reaction of intermediates of general formula III wherein m and $R_{10}$ have the meanings reported above and X is -OH, with compounds of general formula II, wherein $R_4$ ($R_5$) and $R_6$ have the meanings reported above

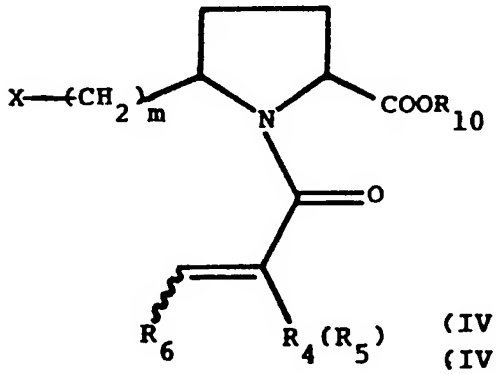



(II)



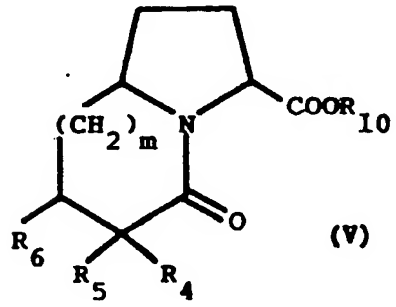

(III)

to give compounds of general formula IV', which are transformed into compounds of general formula IV, wherein X is Br, I, Se-$C_6H_5$



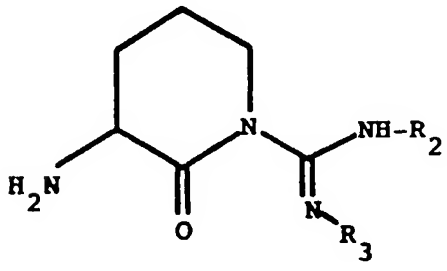
(IV) X = Br, I, Se-$C_6H_5$
(IV') X = -OH

which are cyclized to compounds of general formula V



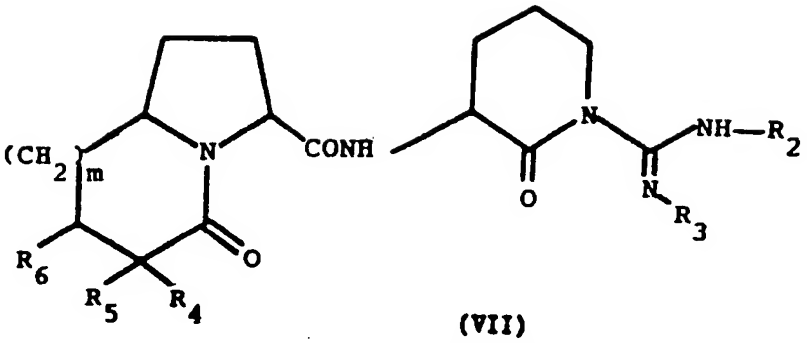
(V)

which are subjected to hydrolysis of the carboxylic group ($R_{10}$ = H) and coupled with intermediates of general formula VI



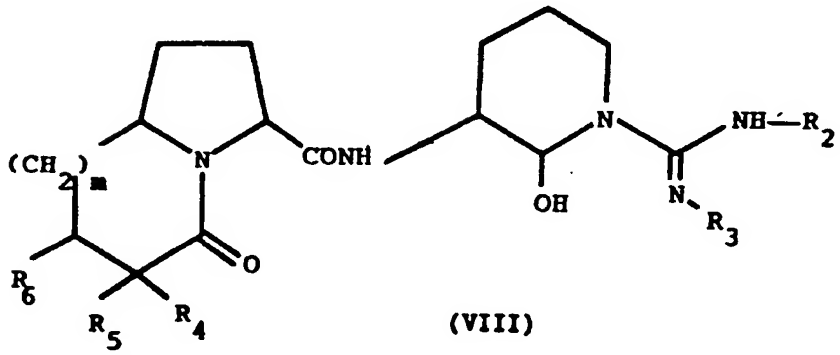
(VI)

to give compounds of general formula VII



(VII)

which are reduced to give compounds of general formula VIII



(VIII)

which are subjected to removal of the protecting groups $R_2$ ($R_3$) and treatment with organic or inorganic acids, to yield compounds of general formula I.

7. The use of the compounds of claims 1-5 as therapeutical agents for use as antithrombotic, anticoagulant or antiplatelet agents.

8. Pharmaceutical compositions containing as active principle an effective amount of one or more compounds of claims 1-5, in admixture with suitable excipients.

# INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/EP 96/03167

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/06 C07D487/04 C07D471/04 A61K31/395
//(C07D487/04,209:00,209:00),(C07D471/04,221:00,209:00),
(C07D487/04,223:00,209:00),(C07D487/04,225:00,209:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | EP,A,0 526 877 (SQUIBB BRISTOL MYERS CO) 10 February 1993 cited in the application see the whole document --- | 1-8 |
| Y | DE,A,41 21 947 (BASF AG) 7 January 1993 see the whole document --- | 1-8 |
| Y | TETRAHEDRON, vol. 49, no. 17, 1993, pages 3577-3592, XP000576111 U.NAGAI E.A.: "Bicyclic turned dipeptide (BTD) as a bêta-turn mimetic;..." see the whole document --- | 1-8 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 December 1996 | 18.12.96 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Groenendijk, M |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 96/03167

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO,A,96 19483 (BIOCHEM PHARMA INC ;DIMAIO JOHN (CA); SIDDIQUI M ARSHAD (CA); GILL) 27 June 1996 see claims 1,2,6-9,30,31,35-38,50-5; table 7 | 1,4,6-8 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/03167

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 96/03167

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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